

ANALYTICAL CHEMISTRY IN A GMP ENVIRONMENT

ANALYTICAL CHEMISTRY IN A GMP ENVIRONMENT

A Practical Guide

EDITED BY

James M. Miller

Jonathan B. Crowther



A WILEY-INTERSCIENCE PUBLICATION
JOHN WILEY & SONS, INC.

New York / Chichester / Weinheim / Brisbane / Singapore / Toronto

DISCLAIMER

SAFETY

The laboratory procedures described in this text are designed to be carried out in a suitably equipped laboratory. In common with many such procedures, they may involve hazardous materials. For the correct and safe execution of these procedures, it is essential that laboratory personnel follow standard safety precautions.

Although the greatest care has been exercised in the preparation of this information, the authors, speaking for themselves, and for the classroom and laboratory instructors, expressly disclaim any liability to users of these procedures for consequential damages of any kind arising out of or connected with their use.

The analytical procedures detailed herein, unless indicated as such, are also not to be regarded as official, but are procedures that have been found to be accurate and reproducible in a variety of laboratories.

APPARATUS

The items of apparatus described in this manual are intended to illustrate proper techniques to obtain a quality analysis and are not to be considered as official and/or required. Any equivalent apparatus obtained from other manufacturers may be substituted.

This book is printed on acid-free paper.®

Copyright © 2000 by John Wiley & Sons, Inc. All rights reserved.

Published simultaneously in Canada.

No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4744. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 605 Third Avenue, New York, NY 10158-0012, (212) 850-6011, fax (212) 850-6008, E-Mail: PERMREQ@WILEY.COM.

For ordering and customer service, call 1-800-CALL-WILEY.

Library of Congress Cataloging-in-Publication Data:

Analytical chemistry in a GMP environment: A practical guide / edited by

James M. Miller, Jonathan B. Crowther

p. cm.

“A Wiley-Interscience publication.”

ISBN 0-471-31431-5

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

CONTENTS

CONTRIBUTORS	xix
FOREWORD	xxi
PREFACE	xxiii

1 The Laboratory Analyst's Role in the Drug Development Process	1
--	----------

Jonathan B. Crowther, William Lauwers, Sagar Adusumalli, and Ponniah Shenbagamurthi

- 1.1. Introduction / 1
 - 1.1.1. The Importance of Analytical Methodology in the Drug Development Process / 1
 - 1.1.2. Interdiscipline Use of Analytical Methodology / 2
 - 1.1.3. Phases of Drug Development / 3
 - 1.1.4. Introductory Summary / 4
- 1.2. Requirements of an Analytical Methodology During the Drug Development Process Release and Stability / 5
 - 1.2.1. Introduction / 5
 - 1.2.2. Discovery Phase / 6
 - 1.2.3. Early Development / 6
 - 1.2.4. Final Development (Phase III) / 9
- 1.3. The Analyst Role in Formulations Development / 12
 - 1.3.1. Overview / 12
 - 1.3.2. Analytical Testing in Formulations Development / 13
 - 1.3.3. Pharmaceutical Excipients / 13
 - 1.3.4. Pharmaceutical Development Summary / 13

1.4.	Review of the Analyst Role in Pharmacokinetics, Toxicology, and Clinical Support /	15
1.4.1.	Introduction /	15
1.4.2.	Bioanalytical Considerations /	15
1.4.3.	Preclinical Pharmacokinetics/ Pharmacodynamics /	18
1.4.4.	Preclinical Safety Studies /	19
1.4.5.	Mass Balance and Metabolism /	21
1.4.6.	Clinical Support /	21
1.5.	Stability Program in Pharmaceutical Industry /	23
1.5.1.	Introduction /	23
1.5.2.	Goals of the Stability Program /	24
1.5.3.	ICH Guidelines on Stability Testing of Drug Products /	24
1.5.4.	Stability Monitoring /	26
1.5.5.	Stability-Indicating Methods /	26
1.5.6.	Pharmaceutical Packaging and Stability /	26
1.5.7.	Stability Summary /	28
1.6.	Chapter Summary /	28
	References /	29

2 Laboratory Controls and Compliance

31

Henry Avallone

2.1.	Introduction /	31
2.2.	Laboratory Management /	33
2.2.1.	Management Responsibility /	33
2.2.2.	Training /	34
2.3.	Laboratory Controls /	35
2.3.1.	Laboratory Records /	35
2.3.2.	Out of Specification/Trend (OOS/OOT) /	38
2.3.3.	Laboratory Deviations/Nonconformances /	39
2.3.4.	Test Methods/Procedures/Specifications /	41
2.3.5.	Calibration and Maintenance /	41
2.4.	Laboratory Compliance /	42
2.4.1.	General Notices /	42
2.4.2.	Method Development /	43

2.4.3.	Method Validation /	44
2.4.4.	Method Transfer /	46
2.4.5.	Auditing the Laboratory /	46
2.4.6.	Use of Outside Testing Laboratories /	47
2.5.	Conclusion /	47
References /		47

3 The USP, ICH, and Other Compendial Methods **49**

Jennifer G. Feldman

3.1.	Introduction /	49
3.2.	USP/NF /	49
3.2.1.	Introduction /	49
3.2.2.	Organization/Overview /	51
3.2.3.	USP/NF and the FDA /	53
3.2.4.	FDA Requirements for Regulatory Submissions/Field Inspections /	53
3.2.5.	Analysis of Excipients/Raw Materials/Drug Substance/Drug Product /	54
3.2.6.	“Meets USP” Labeling /	54
3.2.7.	Methodology /	55
3.2.8.	Accept/Reject Criteria /	55
3.2.9.	Validation /	56
3.3.	European, British, Japanese Pharmacopeias /	56
3.3.1.	EP, Third Edition /	56
3.3.2.	BP /	57
3.3.3.	JP, Thirteenth Edition /	58
3.4.	ICH Guideline /	59
3.4.1.	Introduction/Role of the Guidelines /	59
3.4.2.	Summary of the Guidelines /	60
3.5.	Conclusion /	74
References /		75

4 Statistics in the Pharmaceutical Analysis Laboratory **77**

Alvin J. Melveger

4.1.	Errors Associated with Making Measurements /	78
4.1.1.	Systematic Error /	79

4.1.2.	Random Error /	79
4.2.	Significant Figures and Rounding /	79
4.2.1.	Number of Significant Figures /	79
4.2.2.	Rounding /	82
4.3.	Some Definitions /	84
4.3.1.	Accuracy /	84
4.3.2.	Precision /	85
4.3.3.	Absolute Error /	85
4.3.4.	Relative Error /	86
4.3.5.	Mean /	86
4.3.6.	Average Deviation /	86
4.3.7.	Standard Deviation /	87
4.3.8.	Relative Standard Deviation /	88
4.3.9.	Comparison of Precision and Accuracy /	88
4.3.10.	Standard Error /	89
4.4.	Normal Distribution of Repeated Measurements /	91
4.5.	Student t Test /	92
4.5.1.	Applications of t Test /	93
4.6.	Propagation of Uncertainty (Errors) /	95
4.6.1.	Addition and Subtraction of Uncertainties /	95
4.6.2.	Multiplication or Division of Uncertainties /	96
4.7.	Rejection of Outliers /	97
4.8.	Linear Regression Analysis /	98
4.9.	Quality Assurance/Control /	99
4.10.	Conclusion /	102
	References /	102

5 Basic Analytical Operations and Solution Chemistry

105

Nicholas H. Snow and Wyatt R. Murphy, Jr.

5.1.	Analytical Reagents /	105
5.2.	Sampling /	107
5.2.1.	Obtaining a Representative Sample /	107
5.2.2.	Preparing Samples for Analytical Methods /	107

5.2.3.	Weighing and Balances /	108
5.2.4.	Volumetric Glassware /	110
5.2.5.	Filtering /	111
5.3.	Chemical Equilibrium /	112
5.3.1.	Equilibrium Constants /	112
5.3.2.	Le Chatelier's Principle /	114
5.3.3.	Equilibrium as a Basis for Sample Pretreatment /	116
5.4.	Aqueous Solution Equilibria /	120
5.4.1.	Introduction /	120
5.4.2.	Acids and Bases /	121
5.5.	Reduction–Oxidation Equilibria /	124
5.5.1.	Introduction /	124
5.6.	Karl Fischer Titration /	141
5.6.1.	Karl Fischer Reagents and Reactions /	142
5.6.2.	Karl Fischer Titration Procedures /	142
5.6.3.	Method Development Issues in Karl Fischer Titration /	143
5.7.	Other Methods for Determining Water /	144
5.7.1.	Loss on Drying /	144
5.7.2.	Instrumental Methods /	145
5.8.	Miscellaneous Techniques /	145
5.8.1.	Differential Scanning Calorimetry and Thermal Analysis /	145
	References /	146

6 Spectroscopy

149

Perlette Abuaf and Alvin J. Melveger

6.1.	The Electromagnetic Spectrum /	149
6.2.	Wave-Particle Duality /	149
6.2.1.	Wave Parameters /	150
6.2.2.	Particle Parameters /	151
6.3.	Transitions and Energies /	151
6.4.	Ultraviolet/Visible Spectroscopy /	153
6.4.1.	Electron Type /	153

6.4.2.	Chromophores /	153
6.4.3.	Conjugation and Spectral Shifts /	155
6.5.	Infrared Spectroscopy /	156
6.5.1.	Group Frequencies /	158
6.5.2.	Fingerprinting /	160
6.6.	Beers Law and Quantitative Analysis /	161
6.6.1.	Transmittance /	161
6.6.2.	Effect of Concentration on Transmittance /	161
6.6.3.	Effect of Path Length on Transmittance /	162
6.7.	Instrumentation /	163
6.7.1.	UV/VIS Instrumentation /	164
6.7.2.	IR Instrumentation /	171
6.8.	Raman Spectroscopy /	177
6.8.1.	Raman Instrumentation /	180
6.9.	Near-IR (NIR) Spectroscopy /	180
6.10.	Other Optical and Spectroscopic Techniques /	181
6.10.1.	Polarimetry /	181
6.10.2.	Inductively Coupled Plasma (ICP) and Atomic Absorption Spectroscopy (AAS) /	181
6.10.3.	Mass Spectroscopy (MS) /	182
6.10.4.	Nuclear Magnetic Resonance (NMR) Spectroscopy /	183
6.11.	Summary /	184
	General References /	184

7 Chromatographic Principles

185

James M. Miller

7.1.	Definitions, Terms, and Symbols /	185
7.1.1.	Chromatography /	185
7.1.2.	The Chromatographic Process /	187
7.1.3.	Some Chromatographic Terms and Symbols /	189
7.1.4.	The Normal Distribution /	192
7.1.5.	Asymmetry and Tailing Factor /	193
7.1.6.	Plate Number /	196
7.2.	Comparison of GC and LC /	198

7.3.	Two Important Fundamentals /	199
7.3.1.	Thermodynamics of Chromatography /	199
7.3.2.	Kinetics /	203
7.4.	Some Additional Terms /	212
7.4.1.	Resolution /	212
7.4.2.	Retardation Factor /	213
7.4.3.	System Suitability /	215
7.5.	Summary /	215
	References /	216

8 Gas Chromatography

217*James M. Miller and Harold M. McNair*

8.1.	Some Historical Notes /	217
8.2.	Advantages and Disadvantages /	218
8.3.	Classification of GC /	219
8.4.	Columns /	220
8.4.1.	Stationary Phases /	220
8.4.2.	Column Materials /	221
8.4.3.	Comparison of Column Types /	222
8.4.4.	Solid Supports /	223
8.4.5.	Solid Stationary Phases (GSC) /	224
8.5.	Other Instrument Components /	226
8.5.1.	Carrier Gas /	227
8.5.2.	Flow Control and Measurement /	229
8.5.3.	Sample Inlets and Sampling Devices /	229
8.5.4.	Detectors /	234
8.6.	Temperature Considerations /	241
8.6.1.	Temperature Zones /	241
8.6.2.	Programmed Temperature GC (PTGC) /	243
8.7.	Optimization and Method Development /	248
8.7.1.	Column Selection /	248
8.7.2.	Optimization According to Basic Principles /	248
8.8.	Some Special Topics /	249
8.8.1.	Gas Chromatography/Mass Spectrometry (GC/MS) /	249

- 8.8.2. Derivatization / 250
- 8.8.3. Headspace Sampling / 250
- 8.8.4. USP / 250
- 8.9. Applications / 251
 - 8.9.1. Analysis of Residual Solvents / 251
- References / 252

9 Liquid Chromatography: Basic Overview **255**

Lee N. Polite

- 9.1. Introduction / 255
 - 9.1.1. Importance of HPLC in the Pharmaceutical Industry / 255
 - 9.1.2. Column Versus Planar Liquid Chromatography / 256
 - 9.1.3. Low-Pressure Versus High-Pressure Liquid Chromatography / 256
 - 9.1.4. Advantages and Disadvantages of HPLC / 258
 - 9.1.5. Isocratic Versus Gradient Elution / 258
- 9.2. Column Methods / 261
 - 9.2.1. Normal Phase / 261
 - 9.2.2. Reversed Phase / 262
 - 9.2.3. Ion-Exchange Chromatography / 263
 - 9.2.4. Ion Chromatography (IC) / 264
 - 9.2.5. Ion Pair Chromatography (IPC) / 265
 - 9.2.6. Size Exclusion Chromatography (SEC) / 266
- 9.3. Planar Methods: TLC and PC / 268
 - 9.3.1. Quick and Dirty Procedures / 268
 - 9.3.2. Automation and Special Equipment / 269
 - 9.3.3. High-Performance Thin-Layer Chromatography (HPTLC) / 269
 - 9.3.4. Advantages and Disadvantages of TLC / 269
- 9.4. USP / 270
- 9.5. Instrumentation for HPLC / 270
 - 9.5.1. Pumps / 270
 - 9.5.2. Sample Introduction Devices / 272
 - 9.5.3. Tubing and Connectors / 273

- 9.5.4. Detectors / 274
- 9.5.5. Troubleshooting / 277
- 9.6. Capillary Electrophoresis (CE) / 279
 - 9.6.1. CE Systems / 280

References / 281

10 HPLC Column Parameters 283

Richard Hartwick

- 10.1. Column Equivalency / 284
- 10.2. Review of Chromatographic Parameters / 285
- 10.3. Parameters Necessary for Equivalent Columns / 287
 - 10.3.1. Retentiveness and Selectivity / 288
 - 10.3.2. Peak Shape / 295
- 10.4. Column Efficiency / 295
 - 10.4.1. Resolution / 297
 - 10.4.2. Reduced Plate Heights to Estimate Expected Column Efficiencies / 297
- 10.5. Putting It All Together—Selecting an Equivalent Column / 302
 - 10.5.1. Choosing Equivalent Columns: An Example / 303

References / 307

11 Dissolution 309

Ross Kirchhoefer and Rudy Peeters

- 11.1. Introduction / 309
 - 11.1.1. History / 310
 - 11.1.2. Early Improvements in Dissolution Equipment / 311
- 11.2. Dissolution Basics / 311
 - 11.2.1. Disintegration Tests / 311
 - 11.2.2. Elementary Theory / 313
 - 11.2.3. Practical Aspects / 313
 - 11.2.4. Dissolution Specifications / 314
- 11.3. USP/NF Pharmacopeia General Chapter <711> / 315
 - 11.3.1. Apparatus / 315

11.3.2.	Parameters Affecting the Dissolution Test / 315
11.3.3.	Test Equipment / 322
11.3.4.	Stage Testing / 322
11.3.5.	Calibrators / 323
11.3.6.	Sampling / 323
11.4.	Measurement of the Pharmaceutical Active / 326
11.5.	Analyst Checklist / 328
	References / 328

12 Analytical Method Development for Assay and Impurity Determination in Drug Substances and Drug Products 331

Jonathan B. Crowther, Paul Salomons, and Cindi Callaghan

12.1.	Background / 331
12.2.	Introduction / 332
12.2.1.	Specifications and Their Influence on Method Development / 333
12.2.2.	International Guidelines and Their Influence on Method Development / 333
12.3.	The Method Development Life Cycle—Overview / 338
12.4.	Planning / 338
12.4.1.	Review Company Policy on Method Development/Validation / 338
12.4.2.	Defining the Objectives/Requirements of the Method / 340
12.4.3.	Illustration of Method Requirements / 341
12.4.4.	Information Gathering / 344
12.4.5.	Resource Gathering: Resources/Instrumentation/Materials and Standards / 346
12.4.6.	Documentation: Development Plan / 346
12.5.	Method Development—General Considerations / 347
12.5.1.	Initial Method Development / 347
12.5.2.	Method Optimization / 348
12.5.3.	Method Prevalidation Evaluation / 348
12.5.4.	Robustness / 349
12.5.5.	System Suitability / 350

12.6.	Documentation / 351
12.6.1.	Method Development Report / 351
12.6.2.	Completing Method Development / 353
12.7.	Method Development—Experimental Considerations / 353
12.7.1.	Introduction / 353
12.7.2.	General Components of HPLC Method Development / 353
12.7.3.	Obtaining Sufficient Resolution—Considering Method Requirements / 359
12.8.	Validation Activities / 361
12.8.1.	Documentation—Protocol / 362
12.8.2.	Method Validation—Experimental / 362
12.8.3.	Documentation—Report / 362
12.9.	Analytical Method Transfer / 363
12.9.1.	Documentation—Protocol / 363
12.9.2.	Method Transfer—Experimental / 364
12.9.3.	Documentation—Transfer Report / 364
12.10.	Periodic Review / 364
12.11.	Reference Standards and Samples to Support Stability Indicating Method Development / 365
12.11.1.	Types of Standards / 365
12.11.2.	Handling of Standards / 366
12.12.	Summary / 368
	References / 369

13 Some Principles of Quantitative Analysis

371*James M. Miller*

13.1.	Detector Classifications (Chromatographic) / 372
13.1.1.	Concentration Versus Mass Flow Rate / 372
13.1.2.	Bulk Property Versus Solute Property / 372
13.1.3.	Selective Versus Universal / 374
13.2.	Detector Characteristics / 375
13.2.1.	Noise / 375
13.2.2.	Time Constant / 377
13.2.3.	Cell Volume / 381
13.2.4.	Signal / 381

13.3.	Methods of Quantitative Analysis /	385
13.3.1.	Standards and Calibration /	385
13.3.2.	External Standard /	387
13.3.3.	Area Normalization /	388
13.3.4.	Area Normalization with Response Factors /	388
13.3.5.	Internal Standard Method /	389
13.3.6.	Standard Addition Method /	390
13.3.7.	Summary /	391
13.4.	Additional Topics /	392
13.4.1.	Trace Analysis /	392
13.4.2.	The High–Low Method for HPLC /	392
	References /	392

14 Laboratory Data Systems

395

R. D. McDowall

14.1.	Introduction /	395
14.1.1.	Data and Information Management /	395
14.1.2.	Purpose of Data Systems /	396
14.1.3.	Types of Data System /	396
14.2.	Laboratory Information Management Systems (LIMS) /	397
14.2.1.	A LIMS Has Two Targets /	398
14.2.2.	Benefits of a LIMS /	399
14.2.3.	Regulatory Issues /	400
14.3.	Chromatography Data Systems /	401
14.4.	Analog-to-Digital (A/D) Conversion /	403
14.4.1.	Rationale for A/D Conversion /	403
14.4.2.	Principles of A/D Conversion /	403
14.4.3.	Peak Detection /	408
14.5.	CDS Workflow /	412
14.5.1.	Sequence of Data System Operation /	412
14.5.2.	Instrument Control /	417
14.5.3.	Interfacing CDS to Laboratory Information Management Systems /	418
14.6.	Concluding Remarks /	420
	References /	420

15 Qualification of Laboratory Instrumentation, Validation, and Transfer of Analytical Methods 423

Jonathan B. Crowther, M. Ilias Jimidar, Nico Niemeijer, and Paul Salomons

- 15.1. Introduction / 423
- 15.2. Instrument Qualification / 424
 - 15.2.1. Instrumentation Life Cycle / 425
 - 15.2.2. Introduction—Qualification Versus Calibration / 426
 - 15.2.3. Prospective Versus Retrospective / 426
- 15.3. Instrument Qualification Process—Assembly of the Qualification Team / 429
- 15.4. The Qualification Protocol / 429
- 15.5. IQ Protocol / 430
 - 15.5.1. Installation Qualification / 430
 - 15.5.2. Operational Qualification / 432
 - 15.5.3. Performance Qualification / 432
 - 15.5.4. Ongoing Monitoring / 432
 - 15.5.5. Final Qualification Report / 433
- 15.6. Instrument Qualification Summary / 435
- 15.7. Analytical Method Validation / 435
 - 15.7.1. Introduction to Method Validation / 435
 - 15.7.2. Determining the Characteristics of the Validation / 436
 - 15.7.3. Definitions / 436
 - 15.7.4. Method Validation Documentation / 438
- 15.8. A Systematic Approach to Validation Experimentation / 441
 - 15.8.1. Determination of Method Specificity / 441
 - 15.8.2. Demonstration of Linearity and Range; Determination of Relative Response Factor / 443
 - 15.8.3. Determination of Detection and Quantitation Limit / 446
 - 15.8.4. Demonstration of Accuracy of the Method / 446
 - 15.8.5. Determination of Method Precision / 447
 - 15.8.6. Target Acceptance Criteria / 447
 - 15.8.7. Final Method—Minor Method Refinement / 451

xviii CONTENTS

15.8.8.	Validation Summary /	451
15.8.9.	Method Transfer /	453
15.8.10.	Transfer Documentation /	454
15.8.11.	Method Transfer Protocol /	455
15.8.12.	Method Transfer Experimental /	456
15.8.13.	Transfer Summary and Approval /	456
15.9.	Chapter Summary /	456
	References /	457

APPENDIXES

I	LIST OF SYMBOLS AND ACRONYMS	459
II	GLOSSARY OF TERMS USED IN ICH DOCUMENTS	467
III	UNIVERSAL TESTS, DOSAGE-FORM-SPECIFIC TESTS, AND ACCEPTANCE CRITERIA	473
IV	USP CHROMATOGRAPHIC PHASES	477
	INDEX	483

CONTRIBUTORS

Perlette Abuaf, IRI*Trials Management Center, Annandale, NJ, 08801

Sagar Adusmalli, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Henry Avallone, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Cindi Callaghan, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Jonathan B. Crowther, Janssen Research Foundation, Titusville, NJ 08560-0200

Jenny G. Feldman, Cilag A. G., Hochstrasse 201, 8205 Schaffhausen, Switzerland

Richard Hartwick, PharmAssist Analytical Laboratory Inc., Box 248A, South New Berlin, NY 13843

M. Ilias Jimidar, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium

Ross Kirchhoefer, Gateway Analytical Laboratories, 5703 Hidden Stone Drive, Saint Louis, MO 63129

William Lauwers, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium

Thomas Layloff, Division of Drug Analysis-FDA, 1114 Market Street, Room 1002, St. Louis, MO 63101

R. D. McDowall, McDowall Consulting, 73 Murray Avenue, Bromley, Kent, BR1 3DJ, UK

Harold McNair, Department of Chemistry, Virginia Tech, Blacksburg, VA 24061

Alvin J. Melveger, AJM Technical Consulting, 9 Patrick Court, Flanders, NJ 07836

James M. Miller, Department of Chemistry, Drew University, Madison, NJ 07940

xx CONTRIBUTORS

W. Rorer Murphy Jr., Department of Chemistry, Seton Hall University, South Orange, NJ 07079-2694

Nico Niemeijer, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium

Rudy Peeters, Janssen Research Foundation, Analytical Development, Turnhoutseweg 30, B 2340 Beerse, Belgium

Lee N. Polite, Axion Analytical Laboratories, Inc., 2122 North Bissell, Suite #3, Chicago, IL 60614

Paul Salomons, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Ponniah Shanbagamurthi, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Nicholas H. Snow, Department of Chemistry, Seton Hall University, South Orange, NJ 07079

FOREWORD

The laboratory is an extension of our senses, enabling us to obtain data on substances beyond what we can see with a naked eye and in amounts that our hands could never achieve. These data are compiled into reports and are ultimately used for making decisions, decisions that cannot be confirmed with our unaided senses. The quality of any decision is absolutely dependent on the quality of the data; junk data lead to junk decisions.

The process of acquiring valid data requires properly trained personnel using appropriately calibrated tools. In order to ensure the acquisition of high-quality data, one must be certain that all laboratory tools are suitable for their intended use [i.e., meet their standard operating procedure (SOP) requirements] within their validated limits. In addition, all involved personnel in the data gathering and information generation efforts must have the required knowledge, skills, and abilities (KSAs) to satisfactorily perform their tasks. As has been noted,* this is good business practice and, secondarily, necessary regulatory compliance.

In addition, however, our technological industry continues to churn out an ever-expanding array of almost magical analytical technologies, thereby creating a new group of incompetent laboratory personnel who are not familiar with or trained to use them.

Not surprisingly, these expanding technologies have posed a great and insurmountable challenge to our already much maligned educational system. The college/university curriculum continues with the traditional four-year program where the faculties are supposed to inculcate into the students the usual very strong foundation in the basic knowledge and skills of the science, packaged as a palatable academic program. Because all of this knowledge cannot be rationally delivered in a four-year curriculum, the assurance that those who generate data have the basic KSAs falls to the employers. Management must have confidence that all of the employees in the organization possess the required KSAs to perform their assigned tasks. As competent analysts performing in the laboratory reflect on the adequacy of the first-line management team, incompetent analysts in the laboratory reflect the inadequacy of that team.

Because of severe infractions in the practice of good science and science

* Alan Dinner, personal conversation.

management by several firms, the U.S. Food and Drug Administration found it necessary to issue regulations defining minimum appropriate standards for the performance of nonclinical studies submitted to the agency. This issuance of the “Good Laboratory Practices” regulations made the acronyms “GLPs” and “SOPs” “household” words in laboratories throughout the world. Subsequently, the agency issued the related regulations to provide administrative law guidance for pharmaceutical manufacture in the current good manufacturing practices (CGMPs).

In both cases the regulations were intended to provide broad guidance on appropriate scientific practices in the pharmaceutical industry while not stifling innovation and the evolution to superior practices that still satisfy the requirement. These regulations address many aspects of laboratory operations but only broadly address the skills and abilities of the primary practitioners: the management and bench scientists. This deficit was pointed out in “Analysts: The Unknowns in the Quality Assurance Equation”.[†] That presentation and many subsequent ones focused on the fact that college science graduates do not in general have all the skills required to competently function in an FDA-regulated environment. This poses a crisis for first-line managers who must have absolute confidence that their staff members possess the required KSAs to competently perform the tasks that they are assigned.

In order to ensure that the scientists have acquired the required competencies to adequately perform their assigned tasks, management must establish quality systems structured to provide necessary training and education. It appears that one company, Johnson & Johnson, has taken a direct approach to meeting this challenge by establishing a laboratory analysts training and certification program for its employees.

This text has emerged from that program. It is designed to establish a basic knowledge and skill base in the technologies that are most prevalent in “product control laboratories” of the pharmaceutical industry. The laboratory supervisors who employ the individuals who successfully complete this course can have confidence that they have this well-defined starting point from which they may begin to evolve the individual employee’s skills to journeyman performance levels in their specific organization.

THOMAS P. LAYLOFF

June 1999

[†] T. P. Layloff, AOACI Referee, December 1990, p. 6.

PREFACE

In his Foreword and elsewhere,* Layloff has described the need for more and better training of pharmaceutical laboratory analysts, as perceived by the Food and Drug Administration (FDA). To meet their own needs, the FDA produced a series of self-training aids that could be used in their testing laboratories. Many others are equally aware of the need for training because of the constant introduction of new methods, the increasing demands for better analyses, and the fact that little or no discussion of government regulations is presented in the traditional undergraduate educational program of chemists. Johnson & Johnson recognized this need in the spring of 1996 and began the development of an in-house training course. With the help of academic and industrial consultants, the course was first offered in October 1996 and became the basis for this text.

From the onset, the Johnson & Johnson Laboratory Analyst Training and Certification Program's (LATCP) objective has been to provide lecture and laboratory work in analytical chemical methods and in government regulations (CGMPs) and procedures. The two-week-long course has been presented over 20 times to over 300 analysts, selected from J&J sites around the world. A special facility was constructed for this purpose at the IRI Trials Management Center in New Jersey; more details on the program can be found in a recent trade publication.†

This book is a natural outgrowth of the LATCP and is being published to make the contents of the program available more widely. The level of the material is that which has been found suitable for the participants in the course, who, on average, hold bachelor's degrees in chemistry and already have some experience in the pharmaceutical laboratory; these are typical recruitment criteria for J&J analysts.

The introductory chapter provides an orientation to the drug development process that might not be familiar to new employees in the pharmaceutical industry. Two chapters follow on regulations and compendia. Together these chapters should serve as a basis for understanding the issues in this regulated industry.

* A. S. Kenyon, R. D. Kirchhoefer, and T. P. Layloff, *JAOAC Int.* **1992**, 75, 742–746.

† N. Corkum, H. Avallone, and J. Miller, *Inside Lab Management*, *AOAC*, **2000**, 4, 26–29.

The middle chapters cover some basics of analytical chemistry of relevance to this audience, beginning with statistics and a quick review of equilibrium and solution chemistry. While this material may be too elementary for some, we have discovered that many students in our course are deficient in basic concepts such as significant figures, so such topics are included. The major quantitative techniques covered next are spectroscopy (UV and IR), chromatography (GC, LC, HPLC, and TLC), and dissolution. Of these, HPLC is unquestionably the most important and is the focus of much of the material throughout the book.

The final chapters cover detectors (mainly chromatographic), quantitative analysis, and data systems, plus the special topics of method development (based mainly on HPLC), qualification of instruments, and validation and method transfer.

A multiauthor work such as this one runs the risk of being fragmented and uneven. We have tried valiantly to make it as unified as possible, drawing on our shared teaching experience with the LATCP course. It is, of course, impossible to define a single set of symbols when the topics are so diverse. Appendix I lists the terms and symbols used, noting overlaps in an attempt to keep confusion to a minimum. In chromatography, the IUPAC symbols are used, not those of the USP. This anticipates that USP will eventually adopt the IUPAC system in the spirit of unity and international cooperation. Other appendixes include the terms and some procedures used by another international group, ICH.

Being written to accompany the LATCP course, this book is intended for individual use by laboratory analysts. We have attempted to keep it as succinct as possible and provide sufficient detail, given the wide range of subject matter. The editor and the publisher welcome suggestions and comments for future editions.

We want to acknowledge the two persons who are most responsible for initiating and guiding this project: Hank Avallone, Juanita Hawkins and Nancy Corkum. Their vision, commitment, and support were crucial. In addition, we want to acknowledge the efforts of the LATCP Managers, Pat Magliozzi and Tom Caglioti.

Each of the authors is lauded for her/his efforts to produce a concise chapter within the limitations of time and page length. We also wish to thank the many content reviewers for their valuable time and expertise. Of course, none of this would have been possible without the tedious clerical support by IRI, especially Diane Kelly, Katherine Miles, and Patty Raymondi.

JAMES M. MILLER
JONATHAN B. CROWTHER

*Madison, New Jersey
Titusville, New Jersey
March, 2000*